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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/930,864 | 08/16/2001 | Seth Lederman | C035795/0126287 | 3603 |

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| EXAMINER | |
|---|---|
| WAX, ROBERT A | |
| ART UNIT | PAPER NUMBER |
| 1656 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/22/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/930,864 | LEDERMAN ET AL. | |
| | Examiner | Art Unit | |
| | Robert A. Wax | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Drawings*

1. The drawings were received on January 3, 2007. These drawings are accepted. Examiner appreciates the corrections and withdraws the objections to the drawings.

### *Specification*

2. The objections to the specification in the previous Office action have been obviated by the amendments to the specification; said objections are hereby withdrawn.

### *Claim Rejections - 35 USC § 112, First Paragraph, Written Description*

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 2, 4, 10-14 and 16 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was explained in the previous Office action.

***Claim Rejections - 35 USC § 112, Enablement***

5. Claims 2, 4, 10-14 and 16 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection was explained in the previous Office action.

***Response to Arguments***

6. Applicant's arguments filed January 3, 2007 have been fully considered but they are not persuasive. However, upon further consideration, the arguments with regard to the rejection under 35 USC 102 and its attendant rejection under 35 USC 112, first paragraph, are convincing and those two rejections are hereby withdrawn.

Applicants argue that the written description rejection is factually flawed in that, contrary to Examiner's statements, polypeptides other than SEQ ID No.: 1 are disclosed and that an assay is disclosed and, therefore, one of skill in the art would expect a polypeptide having at least 80% identity to SEQ ID No.: 1 would behave in a similar manner to SEQ ID No.: 1.

Examiner would like to clarify that the statement, "There is no disclosure of any polypeptides other than SEQ ID No.: 1," meant that no polypeptides having at least 80% identity to SEQ ID No.: 1 were disclosed. Of course, applicants are correct that other polypeptides are disclosed but, since none of them have at least 80% identity to

SEQ ID No.: 1 their disclosure cannot be used to provide written description for polypeptides having at least 80% identity to SEQ ID No.: 1. None of the additional fragments of p62 appear to have at least 80% identity to SEQ ID No.: 1 but were an alignment provided showing that one or more of them are, in fact, at least 80% identical to SEQ ID No.: 1 then they would have written description just like SEQ ID No.: 1 does.

Applicants are not completely correct in stating that paragraphs [0038] and [0138] provide an assay to test the activity of the claimed variants of SEQ ID No.: 1 having at least 80% identity thereto. Paragraph [0038] implies that overexpression of SEQ ID No.: 1 inhibits Re1A-induced reporter activity and inhibits NFκB translocation but provides no method of testing that. It is conceivable that one of skill in the art could invent an assay to test that idea but the instant disclosure presents no such assay.

In any event, to qualify as adequate written description, the disclosure must show that the inventors were in possession of the claimed invention. The fact that one might be able to invent an assay to use on a fishing expedition to find variants of SEQ ID No.: 1 that have at least 80% identity thereto does not show that applicants are in possession of any such variants. In fact, the claims do not even require that the variants have the same activity as SEQ ID No.: 1. This does not meet the standard of adequate written description.

With regard to the enablement, Examiner apologizes for including claims that do not recite the 80% limitation in the rejection. The correct claim numbers appear above in the restatement of the rejection.

Applicants argue that there is ample guidance in the specification as to how to make polypeptides that are at least 80% identical to SEQ ID No.: .1. Examiner agrees that one of skill in the art could make the large number of proteins that are at least 80% identical to SEQ ID No.: .1 but points out again that there is no disclosure of which of those would still possess the activity of inhibition of the translocation of activated NF-κB across a nuclear membrane. Apparently another discussion of the Wands factors is warranted since applicants found the previous analysis hurried, factually flawed and apparently too short.

To reiterate, the factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Examiner will again treat each factor, this time in more detail.

First, the amount of experimentation is large because of the large number of polypeptides that have at least 80% identity to SEQ ID No.: 1. The polypeptide having SEQ ID No.: 1 is 393 amino acids long. 80% of 393 is approximately 314, leaving 79 amino acid positions that could be changed to provide at lest 80% identity. Each of the 79 amino acids can be changed to one of the other 19 amino acids so the total number of such mutants is (19! * 79) or 9,609,962,932,297,728,000. This is the number of mutants that have exactly 80% identity to SEQ ID No.: 1. If only 78 positions were

changed the percent identity would be 315/393*100 = 80.16% and the number would be (19! * 78) = 9,488,317,831,888,896,000. The total number of mutants having 80% identity to SEQ ID No.: 1 and those having 80.16% identity to SEQ ID No.: 1 would be 19,098,280,764,186,624,000. When the calculation is repeated for 77 substitutions, 76 substitutions, etc. the total is 384,398,517,291,909,000,000. By any definition this is a large number of possible mutations. This calculation does not take truncations into account or random deletions or additions, all of which would be at least 80% identical to SEQ ID No.: 1. It would take more time to test each one than the time left in the universe's lifetime. Thus, the first Wands factor is satisfied, the amount of experimentation is enormous.

Second, as stated before, the amount of guidance provided by the specification is zero since there is no disclosure of which 20% of the polypeptide having SEQ ID No.: 1 could be changed and still retain the function. Obviously, one of skill in the art would not know how to use mutants possessing changes that eliminate the function. Guidance means providing one of skill in the art with some idea as to what structural characteristics might be responsible for the activity of the protein – in the written description environment we speak of a structure-to-function relationship. Such language has a place in the enablement environment as well since, clearly, not all of the 384,398,517,291,909,000,000 possible mutants will retain the activity. Since it is not possible to make and test each possible mutant, some information as to which mutant(s) to make is required. The instant specification states that the mutants that have at least 80% identity to SEQ ID No.: 1 can be made and tested in accordance with

the information in the specification but there is no discussion of which 79 amino acids may be altered or removed and still retain the activity. The information in the specification directs one of skill in the art to go forth and mutate but discussion of where to mutate and to which amino acid to mutate is conspicuously absent. The very essence of undue experimentation is the trial and error method that applicants are advocating, make each one and test it and only those that have the activity are within the scope of the invention. This is clearly the wrong standard to judge whether undue experimentation would be required to practice the invention. Thus, the second Wands factor is satisfied, the amount of guidance provided is zero.

Third, the specification is totally devoid of any working examples. Not a single polypeptide having at least 80% identity to SEQ ID No.: 1 is disclosed. Contrary to Examiner's previous erroneous statement, other polypeptides are indeed disclosed but these are other fragments of p62, none of which have at least 80% identity to SEQ ID No.: 1. Thus, the third Wands factor is satisfied, no polypeptides having at least 80% identity to SEQ ID No.: 1 are disclosed. Examiner realizes that this paragraph contains only three sentences of explanation but any more would necessarily be only repetitious and, therefore, unnecessary.

Fourth, the nature of the invention, as stated before, is the disclosure of a body of research attempting to establish that p62 (1-393) inhibits the translocation of activated NF-κB across a nuclear [sic, nucleic] membrane with no indication as to the medical significance of that inhibition. Contrary to applicants' argument, Examiner does not believe that medical significance is the *sine qua non* of enablement. However, is does

speak to the "how to use" portion of 35 USC 112, first paragraph. The argument of whether there is a lack of medical significance more properly belongs with the utility rejection and will be further treated below but Examiner stands by his characterization of the nature of the invention. Thus, the fourth Wands factor is satisfied, the nature of the invention, insofar as Examiner perceives it, has been set forth.

The fifth Wands factor is the state of the prior art, which shows that p62 is somehow related to NF-κB and TRAF-3; this information was taken from the specification. The search of this application revealed no information beyond that which is discussed in the specification. Thus, the fifth Wands factor is satisfied, the state of the prior art has been set forth.

The sixth Wands factor is the relative level of skill; the level of skill in this art is very high, that of a PhD scientist with several years' experience. What this means is that the level of detail in the specification need not be as high as it would need to be if the level of skill in the art were lower. Presumably, a person having a lower level of skill would need to be led to conclusions more than a person having a higher level of skill. Thus, the sixth Wands factor is satisfied, the relative level of skill in the art has been set forth.

The seventh Wands factor is the level of predictability of the art is low. The art is replete with examples of how alterations in the sequence of a polypeptide can result in drastically different properties. The example of hemoglobin was given in the previous Office action showing that even a single amino acid change can have drastic effects. If an amino acid in the active site of an enzyme were changed the effect on the enzymatic

activity could be profound. Even so-called conservative substitutions can have dramatic effects. Applicants are as aware of this body of knowledge as Examiner is. Thus, not only is the predictability of which amino acid is substituted low but the effect the location of the substitution is made is also unpredictable. The predictability of the effect of the location of the substitution can be increased by increased knowledge of the structure of the polypeptide as well as the structure to function relationship. For example, subtilisin is an extremely well characterized enzyme and the effect of a substitution in various parts of the molecule can be fairly well predicted. The instant polypeptide is a very different situation, however. The polypeptide having SEQ ID No.: 1 is somewhat characterized as to the structure but not at all characterized as to which part of the structure is responsible for the activity of the polypeptide. Thus, the seventh Wands factor is satisfied, the predictability of the effect of which amino acid is substituted and the location of the substitution are both low.

The final Wands factor is the breadth of the claims. As stated in the previous Office action, the claims are quite broad because of the very different polypeptides encompassed by the polypeptides having at least 80% identity to SEQ ID No.: 1.

After disparaging the statements made by the Examiner in the rejection, applicants finish their arguments with reliance solely on the amount of experimentation. Examiner reminds applicants that the Wands factors must be considered *in toto* and not singly. It is well settled that a single Wands factor cannot be probative of undue experimentation and that is why Examiner has re-presented the arguments regarding all the factors. With the huge amount of experimentation needed, the lack of guidance and

the lack of predictability, in the context of the other Wands factors, clearly results in the conclusion that it would require undue experimentation to make and use the claimed invention.

***Conclusion***

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert A. Wax
Primary Examiner
Art Unit 1656

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